



update

Winter
Volume 25, Issue 2, 2014
News and Views

Radiation Effects Research Foundation Hiroshima and Nagasaki, Japan



Hiroshima
Nagasaki



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RERF Chairman Toshiteru Okubo receiving JISHA Distinguished Service Award (right); see page 10

This newsletter is published twice a year by the Radiation Effects Research Foundation (RERF; formerly the Atomic Bomb Casualty Commission), established in April 1975 as a private, nonprofit Japanese foundation. It is supported by the government of Japan through its Ministry of Health, Labour and Welfare and by the United States through its Department of Energy (DOE), in part by DOE contract DE-HS0000031 with the National Academy of Sciences. RERF became a public interest incorporated foundation on April 1, 2012.

RERF conducts research and studies—for peaceful purposes—on medical effects of radiation and associated diseases in humans, with a view to contributing to maintenance of the health and welfare of the atomic-bomb survivors and to enhancement of the health of all humankind.

Editor-in-Chief: Harry M. Cullings, Chief, Department of Statistics

Technical Editors: Jeffrey L. Hart, Chief, Setsumi Harachi, Tomoe Matsumoto, Public Relations & Publications Office

Editorial Policy

Contributions to RERF Update receive editorial review only and do not receive scientific peer review. The opinions expressed herein are those of the authors only and do not necessarily reflect RERF policies or positions.

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From the Editors

Greetings from the hilltop on Hijiyama in Hiroshima and welcome to the Winter 2014 edition of *RERF Update*. It is early December now and the days are growing very short. We have had some real autumn (chilly) weather suddenly in the last week or so and a sudden loss of foliage from the trees—it appears that winter may arrive after all. The seasonal lighting display on Peace Boulevard in the downtown area is even bigger than before, yet again this year.

With the change in seasons, we have experienced staff changes: the previous technical editor of *RERF Update*, Ms. Tomoe Sugiyama, was transferred to the administrative staff of the Epidemiology Dept. Hers was a short but fruitful stay as editor. Starting with this issue, Mr. Jeffrey L. Hart, Chief of the Public Relations and Publications Office, and some of his staff will take over the technical editor duties.

In this issue of *RERF Update* we talk about opening our doors to several important RERF visitors, including Dr. Susan Lindee, the U.S. author of “Suffering Made Real: American Science and the Survivors at Hiroshima,” who is researching a paper on ABCC’s transition to RERF. A group of doctoral nursing students from Texas Woman’s University listened to a lecture by Dr. Waka Ohishi, Chief of the Clinical Studies Dept., and then met with former ABCC nurses and staff. NASA and other international space agencies held a meeting of the Multilateral Radiation Health Working Group at RERF for four days in mid-October, based on their desire to understand radiation health effects as seen in our research on the health experiences of the survivors of the atomic bombings of Hiroshima and Nagasaki. George Takei, *Star Trek* and internet icon, and his crew, as part of a video series on technology in Japan, visited his ancestral home of Hiroshima in early summer and filmed Dr. Harry M. Cullings explaining GIS technology and

its use in more accurately determining A-bomb survivors’ locations at the time of bombing. Links to the four relevant *Takei’s Take* videos appear on our Facebook page (“Radiation Effects Research Foundation”).



Harry Cullings, PhD

We discuss, in our science articles, recent research taking place at RERF, as well as reports on meetings and workshops held at RERF and a major radiation-related scientific meeting in Las Vegas. Dr. Cullings has provided material in the “Facts and Figures” article about the issue of neutrons from the atomic bombings of Hiroshima and Nagasaki, providing a numerical perspective on the impact of neutrons compared with that of gamma-rays for the radiation doses received by survivors, an issue of enduring concern.

We hope that you enjoy this issue of *RERF Update* as we approach the end of the year and winter, as well as the myriad year-end parties, or *bonenkai*, that accompany this cold but warmly festive season in Japan.

Harry M. Cullings
Editor-in-Chief

Technical Editors
Jeffrey L. Hart
Setsumi Harachi
Tomoe Matsumoto

Fourth Meeting of the Board of Councilors Held at Nagasaki RERF

The fourth meeting of the RERF Board of Councilors (BOC) was held at the Nagasaki Laboratory over the course of two days, June 19–20, 2014. The meeting was attended by seven of the eight councilors, as well as directors, auditors, and the Japanese co-chair of the Scientific Advisory Committee. Representatives of the U.S. and Japanese governments and the U.S. National Acad-

emy of Sciences also attended as observers. Executive Councilor Jonathan M. Samet served as the moderator. In their remarks at the beginning of the meeting, the representatives of the U.S. and Japan governments confirmed their intention to continue support of RERF. The meeting’s major agenda items and discussions are summarized below.

The FY2013 activities, settlement of accounts,



Fourth Board of Councilors meeting held at the Nagasaki Laboratory: Executive Councilor Jonathan Samet (right) and Vice Executive Councilor Ohtsura Niwa (left)

and audit results were reported, with the settlement of accounts approved without any modification. Regarding the FY2014 activity plans, as in the previous year, reports were made on research projects related to the health of A-bomb survivors and of their children; research to review individual radiation doses and elucidate radiation's effects on risk estimates; projects to release research results to the public and to collaborate with other scientific organizations; training programs for Japan and overseas specialists; public information programs; activities necessary to carry out these projects; as well as budget estimates for all the activities. An explanation was also given on the schedule of operations for the Biosample Center, which was established in April 2013.

Scientific Advisory Committee Co-chair Yoichi Gondo reported the committee's recommendations for the activities of the Departments of Epidemiology, Statistics, and Information Technology, issued as a result of its 41st meeting held at the Hiroshima Laboratory March 3–5, 2014. General recommendations were made on research prioritization, improvement of research quality, future plans for reorganization of research departments and personnel training, and enhancement of the global impact of RERF and its contributions to society. RERF's responses to these recommendations were also discussed at the meeting.

Next, based on the various appointment procedures stipulated in the BOC operational regulations, which were set forth this year, two Councilors and two Scientific Advisors were appointed.

Finally, it was decided to hold next year's BOC meeting in Washington, D.C., June 18–19, 2015. On June 17, an informal gathering will be held prior to the BOC meeting, as was the case this year.

List of Participants

Councilors

Dr. Jonathan M. Samet, Professor and Flora L. Thornton Chair, Department of Preventive Medicine, Keck School of Medicine; and Director, Institute for Global Health, University of Southern California

Dr. Ohtsura Niwa, Emeritus Professor, Kyoto University

Dr. Hiroo Dohy, Director, Japanese Red Cross Chugoku-Shikoku Block Blood Center

Dr. Shelley A. Hearne, Visiting Professor, Johns Hopkins Bloomberg School of Public Health, Department of Health Policy and Management

Mr. Masaaki Kuniyasu, Former Ambassador Extraordinary and Plenipotentiary to the Republic of Portugal

Dr. Yasuhito Sasaki, Director General, Clinical Research Center, Shonan Kamakura General Hospital

Mr. James W. Ziglar, Senior Counsel, Van Ness Feldman and Senior Fellow and Advisor to the Board, Migration Policy Institute (Former Sergeant at Arms of the United States Senate)

(Not in attendance)

Dr. James D. Cox, Former Head, Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center

Directors

Dr. Toshiteru Okubo, Chairman/Representative Director

Dr. Roy E. Shore, Vice Chairman and Executive Director

Mr. Takanobu Teramoto, Executive Director

Auditors

Mr. Takashi Kohno, Hiroshima General Law/Accounting Office (Hiroshima CPA Cooperative Office/A&A Tax Accountant Corporation)

Mr. David Williams, Retired Chief Financial Officer, National Academy of Sciences; Certified Public Accountant

Co-chair of Scientific Advisory Committee

Dr. Yoichi Gondo, Team leader, Mutagenesis and Genomics Team, RIKEN BioResource Center

Representatives of Supporting Agencies

Mr. Takeshi Sakakibara, Director, A-Bomb Survivor Support Office, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW)

Dr. Shuichiro Hayashi, Deputy Director, General Affairs Division, Health Service Bureau, MHLW

Mr. Hiroki Yamamoto, Deputy Director, A-Bomb

Survivor Support Office, General Affairs Division, Health Service Bureau, MHLW

Dr. Patricia R. Worthington, Director, Office of Health and Safety, Office of Environment, Health, Safety and Security, DOE

Dr. Isaf Al-Nabulsi, Senior Technical Advisor, Japan Program Manager, Office of Health and Safety, Office of Environment, Health, Safety and Security, DOE

Dr. Kevin D. Crowley, Director, Nuclear and Radiation Studies Board, Division on Earth and Life

Studies, National Research Council, U.S. National Academy of Sciences

RERF

Dr. Robert L. Ullrich, Associate Chief of Research

Dr. Kazunori Kodama, Chief Scientist

Mr. Eiji Akimoto, Chief of Secretariat

Mr. Douglas C. Solvie, Associate Chief of Secretariat

Mr. Yutaka Ogasawara, Associate Chief of Secretariat

Local Liaison Council Meeting Held at Nagasaki RERF

The 23rd meeting of the Nagasaki Local Liaison Council (NLLC) was held in the third-floor conference room at Nagasaki RERF on October 15, 2014. Of 21 Council members, 12 (including four proxies) were in attendance.

Prior to the start of the meeting, Mr. Eiji Akimoto, RERF Chief of Secretariat, introduced the new Council members. After greetings by RERF Chairman Toshiteru Okubo, the proceedings got underway, with NLLC Chairman Dr. Shigeru Katamine (President of Nagasaki University) presiding over the meeting.

Dr. Okubo first reported on the present status of RERF. Vice Chairman and Executive Director Roy E. Shore then spoke about recent research, and Chief Scientist Kazunori Kodama reported on progress made at the RERF Biosample Center in terms of methods related to the preservation and use of biosamples. Dr. Okubo subsequently

reported on progress in the collaborative study with the U.S. National Institute of Allergy and Infectious Diseases (NIAID), followed by Executive Director Takanobu Teramoto explaining RERF's public relations activities.

Each of the above reports was followed by a question-and-answer session and active debate among the Council members, including about such topics as data in RERF's possession and RERF research achievements, resulting in the expression of many valuable opinions.

Dr. Katamine concluded the 23rd NLLC meeting with the following closing remarks: "The objectives of this Council are to compile requests from the local community and have them reflected in RERF's operations. I hope that RERF can fully review and utilize in its future operations the comments and opinions expressed during this meeting."



Scene of the 23rd Nagasaki Local Liaison Council meeting held at Nagasaki RERF

Texas Woman's University Nursing Doctoral Students Visit Hiroshima RERF, Meet with Former ABCC Nurses/Staff

On October 16, 2014, RERF was visited by a group of nursing doctoral students from Texas Woman's University, whose nursing doctoral program is the largest in the United States. The purpose of the group's trip to Japan—part of an elective study-abroad course titled "Historical Research in Nursing—Exploring Japan" that is designed to introduce historical research in the field of nursing, including methodology, significance, analytic techniques, and application—was to highlight the significance of historical nursing research. The Texas Woman's University course aimed at illustrating the process of conducting historical research based on lessons learned following the Hiroshima and Nagasaki A-bombings at the end of World War II and the contribution of those historical events to the current understanding of radiation therapy, occupational safety, civil defense, environmental controls, disaster response, and ethics.

Dr. Sandra K. Cesario, Program Coordinator and Professor, College of Nursing, Texas Woman's University—Houston Campus, led the class comprised of one other university staff member and five doctoral students to Japan. Dr. Cesario indicated that students, through this course, have the opportunity to evaluate personal worldviews, values, and the professional nursing role in the context of the global health community.

After two days in Tokyo, spent speaking to Japanese nursing doctoral students, the group visited Hiroshima. At RERF, after viewing our introductory video, the group was taken on a tour of the facilities and listened to a lecture delivered by Dr. Waka Ohishi, Chief, Department of Clinical Studies, who provided an overview of the history and the conduct of RERF's Adult Health Study (AHS) study since the study's inception in 1958.

After the lecture and lunch, the group of visitors from Texas met with four former Japanese ABCC-RERF employees, three of whom had been nurses attending to the A-bomb survivors, with their period of employment comprising different periods between 1947 and 1989. One of the highlights of the students' trip was said to be the chance to speak with the Japanese women, who had been in Hiroshima or Nagasaki at around the time of the bombings. The students expressed their feelings about how inspirational it was listening to the ABCC employees' stories, given the dif-

ficult circumstances under which they had labored. According to Dr. Cesario about their meeting, "I feel that the Japanese nurses were talking about issues rarely discussed in their day-to-day life."

Touring RERF and hearing of the ongoing research carried out at the institute was reported to be another of the highlights of the Texas Woman's University trip. Afterward, there was said to be unanimous agreement among the members regarding the importance of continuing the scientific work that takes place at RERF. Because of the varied backgrounds and interests of the group members, however, each had her own idea regarding what area of research she found most interesting.

Later that evening, the class enjoyed dinner and discussion with Dr. Susan Lindee, author of "Suffering Made Real: American Science and the Survivors at Hiroshima," who happened to pay a visit to Hiroshima RERF the next day, October 17 (for related information, please refer directly to our Facebook page [Radiation Effects Research Foundation] or by clicking the Facebook link on the RERF homepage, and to page 5 of this edition of *Update*).

The group's three-day trip to Hiroshima, as part of the eight-day total, made the content of the history course "come to life," according to Dr. Cesario. Dr. Cesario indicated that the historical research data from the Hiroshima and Nagasaki atomic bombings, which make a large contribution to scientific understanding of radiation health effects and are used around the world today to shape policies on occupational, environmental and



Texas Woman's University students/staff with former ABCC/RERF nurses/staff

(from left, at rear: Deborah Unruh; Terrylene Ingle; Sabrenda T. Littles; Vicki Brooks; Sandra Cesario; Jen Heathman; Rhonda Kitchen; in front row: Setsuko Fujimoto, Hisae Tanaka, Kiyoko Minato, Merry Y. Uemoto)

other exposures, perfectly fulfill the objectives of the course.

On the day before visiting RERF, the group visited Hiroshima Peace Memorial Park. And, in Dr. Cesario's words, "No trip to Hiroshima would be complete without a trip to the Peace Memorial Park. The entire complex was breathtaking. We found the Hall of Remembrance to be the most moving."

We at RERF are pleased to have been able to

provide relevant historical information related to nursing and medical care, as well as serve as a venue for a bicultural meeting between U.S. and former ABCC-RERF nurses and staff. We feel that RERF is a compelling site for anyone traveling to Hiroshima or Nagasaki as a tourist or student, and we welcome other university study-abroad programs to visit and learn about RERF and our research into the radiation health effects from the 1945 atomic bombings of Hiroshima and Nagasaki.

Dr. Susan Lindee, Author/Scholar, Visits Hiroshima Laboratory to Gather Information for Publication about RERF

Dr. Susan Lindee, Professor and former Associate Dean for the Social Sciences, School of Arts and Sciences, University of Pennsylvania and a visiting research scholar at the Graduate School for International Development and Cooperation (IDEC), Hiroshima University, visited Hiroshima RERF on October 17, 2014. While here, she met and spoke with RERF directors and a number of research scientists as a means of gathering information for a scholarly article on the historical transition from ABCC to RERF, the current status of RERF, and the organization's future with respect to its research on radiation risks.

Dr. Lindee is author of the well-regarded book about the early years of ABCC, titled "Suffering Made Real: American Science and the Survivors at Hiroshima," published by University of Chicago Press in 1994 and reviewed on our Facebook page.

She is particularly interested in describing in her upcoming article about how RERF's research, which she terms "epidemiology without end," might be used in many different scenarios for scientific planning of unknown future risks, such as both technological and natural disasters.

Dr. Lindee's IDEC appointment is scheduled for the period October 1—December 26, 2014. While at IDEC, Dr. Lindee will be teaching a graduate course on Cold War science—a subject she teaches in the United States at the University of Pennsylvania—in a position to which she was appointed by the president of Hiroshima University.

At RERF, Dr. Lindee met first with Chairman Toshiteru Okubo for a conversation about RERF and the A-bomb survivors, followed by interviews of Dr. Roy E. Shore, Vice Chairman and Executive Director; Mr. Takanobu Teramoto, Executive Director; and Dr. Akio Awa, former Chief of Genetics/Associate Chief of Research, who was present in the days when RERF was changing over from ABCC.

After lunch with some of the staff at a local *sushi* restaurant, Dr. Lindee met with Dr. Kazunori Kodama, Chief Scientist; Dr. Robert L. Ullrich, Associate Chief of Research; Dr. Harry M. Cullings, Chief, Statistics Department; and Dr. Eric J. Grant, Assistant Chief, Epidemiology Department. Dr. Lindee joined Dr. John B. Cologne, Senior Scientist, Department of Statistics—who, along with Mr. Jeffrey L. Hart, Chief, Public Relations and Publications Office, organized the visit—for a photo session beneath the banner inside the facilities commemorating ABCC-RERF's 60th anniversary (the organization is now in its 67th year; see photograph at left) and at the front entrance outside, next to the pond of Japanese *koi*.

According to Dr. Lindee, her new project involves the story of ABCC's transition to RERF, "partly because that transition led many involved to articulate why the project was important and



Dr. Susan Lindee (left) and Dr. John Cologne, Senior Scientist, Statistics Dept., inside RERF beneath a banner commemorating ABCC-RERF's 60th anniversary

had to be continued.” She wanted to visit RERF to speak with those directly involved in determining the direction of RERF’s research efforts, because, in her words, “What I feel I have absolutely no understanding of at this stage is the current thinking about the future of RERF—I have seen a few references, but I need to understand much better how things look to those involved today.”

ABCC-RERF is a scientific organization dat-

ing back to 1947, with ABCC becoming RERF in 1975. We are fortunate to be able to provide access to an influential science historian who strives to convey a detailed view of both the historical ABCC and the current RERF. The ABCC era was covered in Dr. Lindee’s historical interpretation of the organization, and we now await the follow-up work that is to cover the contemporary RERF. We wish Dr. Lindee great success in her latest endeavor.

Open House 2014 Held at Hiroshima and Nagasaki RERF

The RERF Hiroshima and Nagasaki Laboratories held their 20th and 18th Open House events, under the theme “Explore and Discover RERF;” on August 5–6 and August 8–9, 2014, respectively.

At the event in Hiroshima, a special exhibit titled “Considering the health effects of low-dose radiation exposure based on atomic-bomb radiation studies” was displayed, in addition to general exhibits reporting recent achievements from our research, which continues because of the understanding and cooperation of A-bomb survivors and numerous others. Many children enjoyed ‘hands-on’ events such as experiments with liquid nitrogen and DNA extraction from broccoli at the science corner, as well as a quiz/stamp rally that they played while walking around the facilities.

On each of the two days, Dr. Masataka Taga, Research Scientist, Department of Radiobiology/Molecular Epidemiology, gave a lecture titled “What is radiation? Basic properties and health effects of radiation” involving background information about radiation. Dr. Yoshiaki Kodama, Chief, Department of Genetics, presented a lecture titled “Radiation exposure and chromosome aberration” concerning radiation-induced chromosomal damage.

Following the aforementioned lectures, Mr. Jeffrey L. Hart, Chief, Public Relations and Publications Office and a translator in the Translation Office, delivered a presentation titled “That’s why translation is fun! The art of English translating in a scientific environment.” The presentation comprised an explanation of the work of translation from Japanese into English, touching on cultural and other differences.

Despite the rainy weather, 889 people visited the laboratory over the course of the two days. Visitors and RERF staff members engaged in active communication at the event, and families with children in particular were prominent throughout the facilities.

At Nagasaki RERF, as in Hiroshima, a special

exhibit titled “Considering the health effects of low-dose radiation exposure based on atomic-bomb radiation studies” was displayed, as were general exhibits introducing methods and results of RERF’s studies.

For the first time at the Nagasaki Laboratory, lectures were presented by research scientists: “RERF clinical studies on A-bomb survivors and children of A-bomb survivors,” by Dr. Ayumi Hida, Acting Chief, Department of Clinical Studies; and



Scene from Open House, Hiroshima: A boy studying cancer cells



Open House, Hiroshima: Dr. Masataka Taga, Research Scientist, Radiobiology/Molecular Epidemiology Dept., speaking to visitors



Open House, Nagasaki: Children filing into Nagasaki RERF

“What is radiation? Basic properties and health effects of radiation,” by Dr. Taga. Based on discussions with Hiroshima staff members regarding the

results of a questionnaire survey from last year, a QR code for cell phones and smartphones was newly added to this year’s flyer advertising the Open House event for the purpose of appealing to college students and adults.

Fortunately, there was no rain over the two days of the Nagasaki Open House, despite the hot and humid weather ahead of an approaching typhoon. A total of 529 visitors to the laboratory for the two days were welcomed by RERF staff members. The questionnaire survey results showed a slight increase in proportion of adult visitors (ages 20 to 59). Furthermore, it was notable that the rate of response to the questionnaire increased to 81.7%, compared with last year’s 74.1%. The survey information is expected to greatly contribute to the planning and holding of the Open House event next year.

Patent Received for Invention “Development and use of an animal model whose internal cells glow when mutated”

Patent #: 5525683

“Development and use of an animal model whose internal cells glow when mutated”

Asao Noda, Assistant Chief, Department of Genetics

Nori Nakamura, Consultant, Department of Genetics

Radiation Effects Research Foundation

A patent was granted to Dr. Asao Noda, Assistant Chief, and Dr. Nori Nakamura, Consultant, both of the Department of Genetics, for their invention titled “Development and use of an animal model whose internal cells glow when mutated.”

Radiation and environmental mutagens are known to cause mutations (alterations of a cell’s DNA) in the cells that make up the body. With the purpose of creating a model mouse that would allow the measurement of mutation risks for somatic/germ cells, the aforementioned inventors succeeded in developing a mouse in which mutated cells glow green *in vivo* to allow easy detection of mutations inside the body, obtaining a patent for this invention. It is expected that the relevant model mouse will be utilized for the benefit of society, such as in environmental monitoring and safety assessment of food, pharmaceuticals, and more.

The relevant June 18, 2014, issue of the Patent Gazette is available at the Industrial Property Digital Library (IPDL), a free-of-charge database of the National Center for Industrial Property Information and Training.



Patent certificate

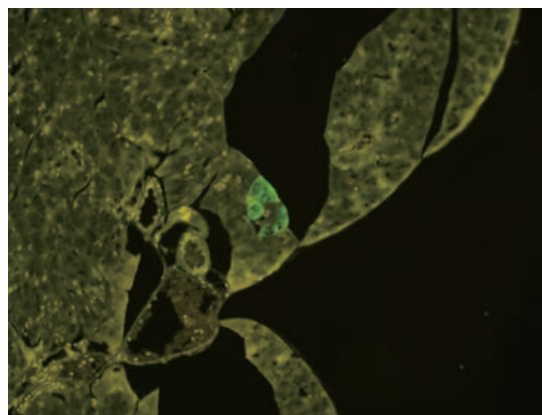


Image of mutated cells illuminated in tissue

Staff News

Mieko Kodaira's term as Chief of the Laboratory of Biochemical Genetics, Department of Genetics, expired on June 30, 2014. She was reappointed as Adjunct Specialist (research scientist) effective July 1, in order to continue her research at the same laboratory.

Fukiko Mitsui joined the Department of Clinical Studies as a research scientist as of October 1, 2014. She introduces herself in the following section.

Fukiko Mitsui, MD, PhD

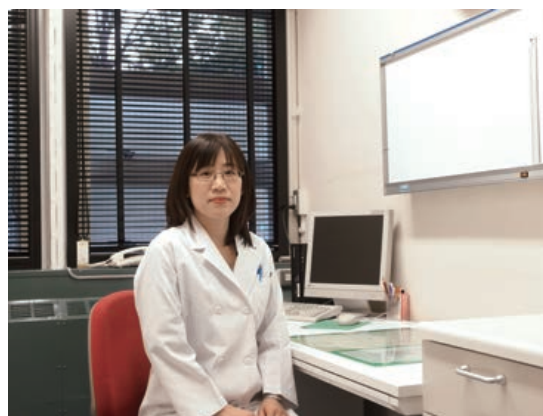
On October 1, 2014, I assumed the position of fixed-term research scientist at the Department of Clinical Studies in Hiroshima.

Starting in 2000, after graduating from the Faculty of Medicine, Hiroshima University, I served as a resident at the Hiroshima University Hospital and the Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital for two years. I subsequently joined the Department of Internal Medicine I (present-day Department of Gastroenterology and Metabolism), Faculty of Medicine, Hiroshima University, worked for the JA Hiroshima General Hospital, and in 2005 entered the Graduate School of Biomedical & Health Sciences, Hiroshima University.

The theme of my doctoral research at the graduate school was: "Study of the therapeutic effectiveness of nucleotide analogues (antiviral drugs) for hepatitis B." With the advent of nucleotide analogues, dramatic progress has been made in the area of treatment for hepatitis B. Since such treatment is ineffective in some cases, however, I

studied the factors affecting antiviral effectiveness. Upon completion of my doctoral degree based on this research, I worked at the Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital until I left the hospital for the birth and care of my child. In April 2013, I assumed the post of visiting research associate at the RERF Department of Clinical Studies in Hiroshima to engage in health examination work.

I was hired as a fixed-term research scientist at the Department of Clinical Studies in Hiroshima most recently to also engage in research. I hope to contribute to the department's research activities, while studying the long history of RERF and its research achievements. Since there are so many things I need to learn, I would appreciate everyone's continued support.



Research Scientist Fukiko Mitsui in her office at Clinical Studies Dept., Hiroshima RERF

Visiting Student Fellows

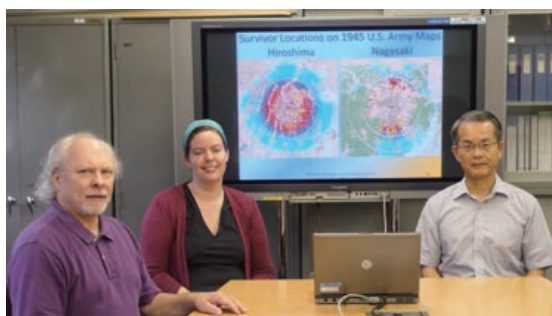
Kaitlin Kelly-Reif (Training period: June 17–August 18, 2014)

As a summer fellow of the Japan Society for the Promotion of Science (JSPS), I studied at RERF under the guidance of Dr. Harry M. Cullings, Chief, Department of Statistics. While at RERF, I conducted a geostatistical estimation of residual radiation in the area near the hypocenter of the Hiroshima atomic bomb as well as the Koi-Takasu area in the western part of Hiroshima, using historical surveys and spatial hierarchical modeling techniques.

I grew up in Sacramento, California, where I developed my interest in health sciences at an early

age by monitoring air quality at my high school as a volunteer with the American Lung Association. I attended college at UCLA, where I continued my studies in environmental science, conservation biology, and geographical information systems (GIS). After college, I traveled extensively and then lived in the Republic of Cameroon, in Africa, working for an environmental research group. In 2012, I moved to Chapel Hill, North Carolina, where I currently live. I am pursuing a Ph.D. in environmental and occupational epidemiology at the University of North Carolina at Chapel Hill.

Although I am training as an epidemiologist, I have a strong interest in geospatial statistics and



Kaitlin Kelly-Reif during training at RERF, with Dr. Harry Cullings (left) and Mr. Takanobu Teramoto, Executive Director (right)

environmental modeling. These are important tools with the potential to improve exposure information for many different types of epidemiological studies. Working with Dr. Cullings has given me a great introduction to these methods, knowledge that is sure to enhance my future doctoral research. Attending meetings in the Epidemiology and Statistics Departments has provided me with valuable insight into the long-term health consequences of the atomic bombings. I also have developed a more nuanced understanding of the historical, social, and methodological challenges that radiation scientists face in addressing radiation risk.

I have enjoyed my time working at RERF, and also enjoyed my time exploring Japan's natural beauty. I am particularly fond of the Japan Alps and the Shimanami Kaido bicycle route. I look forward to returning to Japan in the near future for more research and travel.

I am grateful to RERF, JSPS, and the National Science Foundation for making this valuable opportunity possible. In addition to research support, JSPS provided an excellent language and culture orientation for all its summer fellows. I would like to thank Dr. Cullings in particular for his assistance and expertise on this project. I would also like to thank my friends and colleagues at RERF who have helped me throughout my time here.

Yoshifumi Kondo (Training period: October 1, 2014–January 20, 2015)

I am a visiting research fellow at RERF's Department of Radiobiology/Molecular Epidemiology (R/ME). At the same time, I study medicine

at Hiroshima University and, as such, have the privilege of undergoing training at RERF as part of the university's medical training program provided in the latter half of the fourth year of the program.

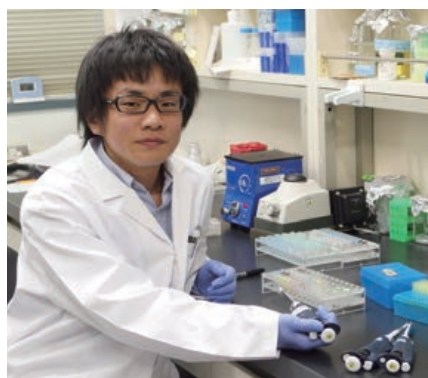
I learned about RERF's plan to accept trainees when Dr. Toshiteru Okubo, RERF Chairman, visited our university to give a lecture, and I decided to seek the valuable opportunity. I am studying under Dr. Kengo Yoshida, Research Scientist of the same R/ME Department, since I am particularly interested in biochemistry and hematology among all the other interesting classes at the university, among which I am having such difficulties choosing a future career path.

I was born and raised in Hiroshima and have thus known about RERF on Hijiya since I was in elementary school. However, I feel that this training in particular has been instrumental in teaching me about the history and role of RERF.

I am committed to doing my best to grow during the training period under the mentorship of the R/ME members, although I have little experience in or knowledge of work related to lab experiments.

At my university, I retired last year from a motorsports club, where I had many good friends, and am now a member of a pop music club. I like motorsports and enjoy going for a drive to the beach and the mountains while listening to my favorite music.

In conclusion, I am grateful for the thoughtfulness of everyone at RERF to make sure that I gain a footing not only in research activities but also in life at RERF. I ask for your continued support.



Yoshifumi Kondo in his office as student trainee at Radiobiology/Molecular Epidemiology Dept.

Award Received by RERF Chairman

RERF Chairman Toshiteru Okubo Receives JISHA Distinguished Service Award

RERF Chairman Toshiteru Okubo was recently honored as the recipient of the 2014 Distinguished Service Award of the Japan Industrial Safety and Health Association (JISHA). The award ceremony took place during the general conference of the 73rd National Industrial Safety and Health Convention, held at the Hiroshima Prefectural Sports Center on October 22, 2014.

Starting with his work at Japan's University of Occupational and Environmental Health in his previous post, Dr. Okubo has endeavored to establish a system of specialization for occupational physicians, whose role is to protect worker safety and health, in order to enhance the professionalism and improve the status of this particular group of physicians. He has made significant contributions for more than 30 years to the development of occupational health and the prevention of workplace accidents in Japan. Chairman Okubo's considerable achievements were acknowledged with the presentation of this year's JISHA Distinguished Service Award.

To commemorate Dr. Okubo's prestigious award, Mr. Takanobu Teramoto, Executive Director, Dr. Kazunori Kodama, Chief Scientist, and Mr. Eiji Akimoto, Chief of Secretariat, organized a gathering at the traditional Japanese restaurant

Mitaki-So, in Nishi-ku, Hiroshima, on October 24. This festive occasion was attended by RERF colleagues and distinguished guests, including President Ginji Endo of the Japan Society of Occupational Health, RERF Councilor Hiroo Dohy, and RERF Auditor Takashi Kohno.



RERF Chairman Toshiteru Okubo backstage, with the JISHA Distinguished Service Award

Fourth Meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors Held at Hiroshima RERF

**Waka Ohishi, Chief
Department of Clinical Studies, Hiroshima**

The fourth meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors was held at the RERF Hiroshima Laboratory Auditorium on May 15, 2014, in order to deliberate on a report regarding progress of the Longitudinal Clinical Study of the F₁ Offspring of A-bomb Survivors and draft revisions of the informed consent form and explanatory documents in accordance with the revisions of the Ethics Guidelines for Human Genome/Gene Analysis Research.

In the previous health effects study of the children of A-bomb survivors, a mail survey of 24,673 subjects and a clinical health study of 11,951 subjects were conducted between 2000 and 2006 to determine the relationship between parental radiation exposure and the prevalence of multifactorial diseases among their children. In that study, we found no evidence showing an increase of disease risks related to parental radiation exposure, either in analyzing six multifactorial diseases (hypertension, hypercholesterolemia, diabetes, angina pectoris, myocardial infarction, and stroke) together or in analyzing the individual multifactorial diseases separately. However, continuation of the study was recommended because in such prevalence studies there tends to be a bias related to decision-making among the participants regarding whether or not to undergo health examinations. Moreover, at that time the average age of the subjects, about 49 years, was still relatively young. In response to this recommendation, on November 24, 2010, the Longitudinal Clinical Study of the F₁ Offspring of A-bomb Survivors was initiated for about 12,000 subjects.

The meeting's proceedings began with greetings and the introduction of committee members by RERF Chairman Toshiteru Okubo, which was followed by greetings from committee Chairman Tadao Shimao. Dr. Ohishi reported on the progress made in the Longitudinal Clinical Study of the F₁ Offspring of A-bomb Survivors during the three years since its initiation. Measures have been taken since the year before last to include people who remained undecided about undergoing examination and people whose address was unknown. Letters requesting participation were re-sent to those who had refused to undergo examination, and as a result, the participation rate including expected participants has improved steadily, increasing from 69.2% in the first year to 76.0% and 76.8% after

two and three years, respectively. Future plans for the longitudinal study were also explained: the first examination cycle (four years) concluded at the end of November 2014, and preliminary calculations of the prevalence and incidence of individual multifactorial diseases began in December 2014 to determine whether there are sufficient numbers of cases for statistical analysis.

As for the ethics agenda item discussed in accordance with revisions made in February 2013 to the Japan Ethics Guidelines for Human Genome/Gene Analysis Research, Dr. Ohishi explained policies concerning how to deal with requests from health examination participants for the withdrawal of informed consent, as well as draft revisions for the consent form concerning storage and use of samples, related explanatory note, and for the form of request for discontinuation. Animated discussions were held, with committee Vice Chairman Hiraku Takebe serving as moderator. As a result of the discussions, it was decided that the draft revisions required further review, and we were requested to reconsider them based on the opinions of the committee members. The meeting concluded with a summary delivered by Dr. Shimao and closing remarks and words of appreciation by RERF Vice Chairman Roy E. Shore.

Due to our efforts to achieve a participation rate of 80% (about 10,000 individuals), the number of participants visiting RERF to undergo health examinations in the first examination cycle of the longitudinal clinical study is projected to exceed 9,500. We will continue our efforts to ensure that the study participants understand the significance of the longitudinal clinical study and encourage



Fourth meeting of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb survivors held at the Hiroshima Laboratory

their continued involvement in the study by sending letters requesting participation and contacting them by telephone.

Members of the Scientific and Ethics Committee for the Clinical Study of the F₁ Offspring of A-bomb Survivors

Dr. Tadao Shimao (Chairman), Consultant, Japan Anti-Tuberculosis Association

Dr. Hiraku Takebe (Vice Chairman), Fellow, Kinki University Atomic Energy Research Institute

Dr. Hirotsugu Ueshima, Special Contract Professor, Lifestyle-Related Disease Prevention Center, Shiga University of Medical Science

Dr. Takashi Kawamoto, Professor, Graduate School of Education, The University of Tokyo

Mr. Shinsuke Kimura, Attorney, Kimura Shinsuke Law Office

Dr. Hideo Sasaki, Professor, Department of Nutritional Sciences, Faculty of Human Ecology, Yasuda Women's University

Dr. Steve Wing, Associate Professor, Department of Epidemiology, School of Public Health, University of North Carolina

Dr. Kazuo Tajima, Director, Aichi Cancer Center Research Institute

Dr. Masao Tomonaga, Director, Japanese Red Cross Nagasaki Atomic Bomb Hospital

Dr. Taisei Nomura, Professor Emeritus, Osaka University

Dr. Norihiko Hayakawa, Professor Emeritus, Hiroshima University

Dr. Yoshimitsu Fukushima, Dean, Shinshu University School of Medicine

Dr. Katsumi Furitsu, Assistant Professor, Department of Genetics, Hyogo College of Medicine

Dr. Eiji Maruyama, Professor, Graduate School of Law, Kobe University

RERF Participants

Dr. Toshiteru Okubo, Chairman

Dr. Roy E. Shore, Vice Chairman and Executive Director

Mr. Takanobu Teramoto, Executive Director

Dr. Robert L. Ullrich, Associate Chief of Research

Dr. Kazunori Kodama, Chief Scientist

Mr. Eiji Akimoto, Chief of Secretariat

Mr. Douglas C. Solvie, Associate Chief of Secretariat

Members, Working Group for the Clinical Study of the F₁ Offspring of A-bomb Survivors

Research Scientists, Department of Clinical Studies

Fifth Epidemiological Training Workshop for Biologists

Ritsu Sakata, Associate Senior Scientist Department of Epidemiology, Hiroshima

The fifth Epidemiological Training Workshop for Biologists, sponsored by the Council of Radiation Effects Research Organizations*, was held August 25–26, 2014, at the Auditorium of the Hiroshima Laboratory, and 34 people, 11 from RERF, attended. During the reception at last year's workshop, there was a request that young researchers be given more opportunities to express their opinions during workshop sessions. Thus, at the start of this year's event, young researchers and self-designated "beginners" were encouraged to speak up throughout the workshop events. Even when a discussion extended beyond its scheduled time, this year's event did not conclude until questions and debate had finished.

To help establish a common vocabulary for all attendees, on the first day Dr. Ritsu Sakata, Associate Senior Scientist, Hiroshima Department of Epidemiology, gave a lecture titled "Epidemiology for non-specialists," and explained epidemiologi-

cal terms and described typical research methods. This was followed by the lectures "Recent results from the Life Span Study" (Dr. Sakata), "Genetic effects in atomic bomb survivors" (Dr. Yoshiaki Kodama, Chief, Department of Genetics), and "The past, present, and future of radiation effects studies among the atomic bomb survivors exposed *in utero*" (Dr. Nori Nakamura, Consultant, Department of Genetics), in which were presented research results of the RERF follow-up study populations of the Life Span Study (LSS), the study of children of A-bomb survivors, and the *in utero* study.

In a subsequent lecture titled "Natural radiation risk for leukemia," Dr. Atsuko Sadakane, Associate Senior Scientist, Hiroshima Department of Epidemiology, explained appropriate ways of reading and understanding epidemiological papers. In a lecture titled "Radiation exposure and thyroid cancer," Dr. Misa Imaizumi, Chief, Division of

Radiology, Chief, Division of Clinical Laboratories, Nagasaki Department of Clinical Studies, spoke about thyroid cancer, a topic of special interest given the nuclear power plant accident in Fukushima.

Following the first day's meetings, most workshop participants attended a reception, which Chief Scientist Kazunori Kodama also joined. The gathering's enjoyable atmosphere allowed for relaxed interaction to take place among the researchers.

On the second day, three new topics were addressed, building on discussions arising from the basic knowledge presented on the opening day. Dr. Nakamura presented two lectures: "What is the meaning of 'no indication of an age at exposure effect on breast cancer'?", and "Does radiation induce cancer or accelerate cancer onset?" Dr. Otsura Niwa, a specially appointed professor at Fukushima Medical University, gave a talk titled "Biological science paradigms from radiation biology."

This series of workshops aims at enhancing communication between biological and epidemiological researchers based on the use of commonly understood, rather than arcane, terminology. Now, after several workshops have been held, the gatherings feature participants actively raising questions and speaking their minds, hinting at the fruitful result of the consecutive workshops. Even so, midway through the event this time, only researchers well versed in RERF studies participated in the discussions. At that point, we felt it necessary to provide more descriptions using general terms, not the specialized language we use typically, and to give appropriate explanations in order to ensure that participants attending the workshop for the first time could also join in the dialogue.

At the close of the workshop, opinions were sought about the future of this workshop series. Attendees identified a variety of goals and objec-

tives for their participation and suggested a number of desirable topics for the future, including themes such as "how radiation dose estimates are obtained," "carcinogenesis research," "a mathematical model of carcinogenesis," and "comparisons with epidemiological research in other fields." It was also suggested that attendees receive practical training in analysis. There were requests for a repeat of explanations of basic epidemiology and appropriate techniques for reading and understanding epidemiological papers. Some attendees asked about the possibility of having a retreat or expanding the schedule, but considering the necessary budget and the inconvenience for participants traveling from afar, it may be necessary to continue the current practice of ending the workshop after a day and a half. We need to review alternatives, such as distributing basic information on the website or sending relevant materials in advance to make sure that participants can study beforehand, and allocating more workshop time for requested topics.

I hope to modify the format of the next workshop based on the opinions and requests raised by this year's attendees. I would like to express my appreciation to all those who participated, those who gave lectures, and the staff members of the General Affairs Section and the Department of Epidemiology who supported the holding of the workshop.

*The Council of Radiation Effects Research Organizations was established to develop understanding among radiation research organizations and strengthen their alliance. The Council includes representatives of the Institute for Environmental Sciences, Kyoto University, Nagasaki University, Hirosaki University, Hiroshima University, Fukushima Medical University, National Institute of Radiological Sciences, and Radiation Effects Research Foundation (arranged according to the Japanese syllabary).



Participants of the fifth Epidemiological Training Workshop for Biologists

Meeting of the Conference on Radiation and Health Held in Las Vegas

**Harry M. Cullings, Chief
Department of Statistics**

The Conference on Radiation and Health (CRH), formerly the ASA Conference on Radiation and Health, recently held a successful meeting September 21–24, 2014, in conjunction with the annual meeting of the Radiation Research Society (RRS) in Las Vegas, Nevada, U.S.A. This is a new affiliation for the CRH and its success was both important and auspicious for the conference's future.

The CRH was affiliated with the American Statistical Association (ASA) for many years, starting at its inception in 1981. For the first few years the meeting was held on a yearly basis at the Coolfont Conference Center in Berkeley Springs, West Virginia, a small resort in the mountains northwest of Washington, D.C., and was often called the "Coolfont" meeting. It was a small, highly focused gathering held in a somewhat secluded area to allow for maximal interaction among the participants. Over the years, it came to be held on a biannual basis in various similarly secluded locations in the eastern and western U.S., but always under the aegis of the ASA. It was typically sponsored by a number of organizations with an interest in promoting the scientific investigation of radiation health effects, including various government agencies.

After the 2012 meeting of the ASA-CRH in Kennebunkport, Maine, the ASA decided to discontinue its involvement with the meeting, and the CRH organizing committee sought to affiliate with a new group that could provide the financial guarantees and other backing necessary to secure a venue and arrange such a meeting. Fortunately, particularly due to the diligence of organizers such as Dr. Dan Stram (University of Southern California), Dr. Lydia Zablotska (University of California, San Francisco), Dr. Cecile Ronckers (Emma Children's Hospital/Academic Medical Center, the Netherlands), and Dr. Alice Sigurdson (U.S. National Cancer Institute), the CRH was able to arrange an affiliation with the RRS and a meeting held in conjunction with the society's annual meeting.

The purpose of the contemporary CRH is to provide the latest information on new methodologies and research in the health effects of radiation exposure from diverse perspectives with the goal of creating an understanding of the topic

from a more global perspective. These viewpoints include the laboratory, the clinic, and epidemiologic studies of populations exposed to ionizing radiation from occupations, medical therapy, or environmental contamination. The research scientists in attendance were statisticians, epidemiologists, physicians, risk assessors, psychologists, biologists, and physicists working in radiation research and dosimetry.

The meeting seems to have been a clear success. There were joint sessions, and attendees could participate in both CRH and RRS sessions. There was a complementarity in that the epidemiological and radiation protection emphases of the CRH fitted in well with the physical, molecular/biological, and radiation oncology emphases of the RRS meeting. In recent years, the CRH has also expanded its portfolio to include travel support and mentoring for young investigators (Early Stage Radiation Investigators = ESRI).

This year's CRH was supported by various organizations including the U.S. Department of Energy and other federal agencies. RERF has long been involved with and has supported the CRH, and the author has been a member of the CRH organizing committee for several years. This year, RERF contributed support in kind by supporting travel for several invited speakers from RERF. The meeting was attended by numerous researchers from RERF, many of whom were invited speakers or presented posters at CRH, including Drs. Roy E. Shore (Vice Chairman), Harry M. Cullings (Dept. of Statistics), Eric J. Grant (Dept. of Epidemiol-



Dr. Kyoji Furukawa, Research Scientist, Statistics Dept., presenting at the Meeting of the Conference on Radiation and Health in Las Vegas

ogy), Atsuko Sadakane (Dept. of Epidemiology), Kyoji Furukawa (Dept. of Statistics), Ritsu Sakata (Dept. of Epidemiology), and Munechika Misumi (Dept. of Statistics). Other RERF researchers presented at RRS and were able to attend the CRH and joint CRH-RRS sessions, including Drs. Robert L. Ullrich (Associate Chief of Research), Kazunori Kodama (Chief Scientist), Ikuno Takahashi (Dept. of Clinical Studies), Norio Takahashi (Consultant, Associate Chief of Research Office), and Yasunari Satoh (Dept. of Genetics). The CRH organizers graciously scheduled a late-breaking joint CRH-RRS session on the recent joint RERF-NCI work on cancer incidence. There was also a joint CRH-RRS session on Fukushima and Chernobyl, which included an invited speaker from Keio University in Japan, Dr. Yutaka Kato, who spoke on the psychosocial aspects of the earthquake, *tsunami*, and nuclear power plant disaster in Fukushima.

The conference keynote speaker, Dr. Flora E. van Leeuwen, delivered the evening banquet address titled “From old radiation treatment records to survivorship care plans: an exciting

journey.” The seven scientific sessions were titled (A) Radiation-induced long term non-cancer risks: EU projects ‘CEREBRAD’ and ‘PROCARDIO,’ (B) Solid cancer incidence among atomic bomb survivors, updated analysis through 2009, (C) Late effects of radiotherapy: new dosimetric approaches in epidemiologic studies, (D) CT scans and cancer risks: new results and methodological issues, (E) Genetic issues in radiation epidemiology, (F) Bridging mechanisms of radiation action at low doses and human risk, and (G) Fukushima and Chernobyl.

Although the nature of the CRH meeting may change somewhat in future years, due to its being collocated with another major scientific meeting, it appears that supporters of the CRH can look forward to more exciting meetings in the future.

The author is indebted to Dr. John B. Cologne, Senior Scientist, Department of Statistics of RERF, who amazingly had preserved a copy of the program of Coolfont IV, which he and the author attended as graduate students 30 years ago, in 1984.

International Space Agencies Visit Hiroshima RERF to Further Understanding of Health Effects from Radiation in Space

RERF recently had the opportunity to serve as host for the annual meeting of the Multilateral Radiation Health Working Group (RHWG) during the period October 20–23, 2014. The roughly 20 RHWG members included personnel from the U.S. National Aeronautics and Space Administration

(NASA), the Japan Aerospace Exploration Agency (JAXA), the Canadian Space Agency (CSA), the European Space Agency (ESA), and the Russian Federal Space Agency (FSA). As its aim is to investigate radiation and health issues, the RHWG asked to consult with RERF to take advantage of



Dr. Michael Barratt, MD/(NASA) Physician Astronaut, speaking via Skype to RHWG and RERF participants about spaceflight

our internationally recognized expertise and leadership in this area.

The opening session of the meeting, October 20, included welcoming remarks by RERF Chairman Toshiteru Okubo and greetings by a JAXA representative. The highlight of the morning was a videoconference presentation provided by Dr. Michael Barratt, MD/Physician Astronaut, NASA Johnson Space Center, who spoke from the United States on the theme of human spaceflight and his experiences on the International Space Station (ISS), including the numerous challenges while working in space such as radiation exposure, appropriate exercise, food choices, viral infections, and limits to the kind of research that can be conducted on board.

Other presentations throughout that day's briefings session involved mainly radiation and health considerations in space, including a presentation by JAXA on its radiation health activities. NASA then spoke on the theme of space radiation health, protection, and operational support, and separately, on its radiation health research portfolio, while ESA presented on European activities related to radiation protection in space. CSA added information about its radiation health activity reviews. In the late afternoon, the RHWG working group members visited Hiroshima Peace Memorial Park and the Peace Memorial Museum, followed by a reception that was hosted by RERF at a popular Western-style restaurant in the downtown of Hiroshima.

The following day, October 21, was dedicated to presentations by RERF staff, starting with welcome remarks by Dr. Robert L. Ullrich, Associate Chief of Research. Dr. Kotaro Ozasa, Chief, Epidemiology Department, introduced RERF and its LSS and AHS cohorts; Dr. Harry M. Cullings, Chief, Statistics Department, gave a presentation on the RERF dosimetry system; Dr. Eric J. Grant, Assistant Chief, Epidemiology Department, spoke on radiation risks of breast and other solid cancers; Dr. Ritsu Sakata, Associate Senior Scientist, Epidemiology Department, presented information about her research into radiation risks of lung cancer and stomach cancer, both with and without adjustment made for smoking; and Dr. John B. Cologne, Senior Scientist, Statistics Department, spoke on radiation risk of liver cancer, including the aspects of interaction, mediation, and uncertainty.

The meeting resumed following a lunch held in the reception room of the RERF Hijiyama Hall. Dr. Waka Ohishi, Chief, Clinical Studies Department, explained radiation risks of cardiovascular diseases; Dr. Michiko Yamada, Chief, Division of Radiology, Clinical Studies Department, elaborated on radiation effects in relation to cognitive changes and other central nervous system issues; Dr. Roy

E. Shore, Vice Chairman and Executive Director, spoke on issues in modeling radiation risks; and Dr. Ullrich concluded the session with his elaboration of tissue quality factors derived from experimental studies. The day ended on a relaxed note, with the participants and other support staff attending a dinner hosted by JAXA at a *tofu* restaurant in the local Hijiyama area.

The third day, October 22, comprised RHWG discussions about its administrative business and other items, in what was a closed session. The fourth and final day, October 23, concluded at around noon, after a review of the meeting agenda and a discussion, followed by an informal media gathering in the early afternoon at RERF that centered on a presentation offered by Mr. Edward Semones, NASA Spaceflight Radiation Health Officer, NASA Johnson Space Center.

Mr. Semones' presentation to the media focused on the importance of RERF's radiation health effects research in terms of NASA attempts to overcome the health impacts of exposure to ionizing radiation from the space environment, in particular when considering its future aim to keep humans in space over a long duration on such projects as its asteroid capture mission and manned mission to Mars. Mr. Semones closed his presentation with the sentiment that by collaborating with RERF, NASA and other such agencies can explore space while reducing the impact of radiation health effects on astronauts.

The meeting provided RERF with an excellent opportunity to showcase its detailed knowledge of radiation health effects based on its research on the health experience of the survivors of the atomic bombings of Hiroshima and Nagasaki. We hope for continued collaboration with the RHWG and these renowned space agencies in the future.



Mr. Edward Semones, NASA Spaceflight Radiation Health Officer, addresses a group of journalists in a media forum following conclusion of the RHWG meeting

Inverse Associations between Obesity Indicators and Thymic T-cell Production Levels in Aging Atomic-bomb Survivors*

Kengo Yoshida

Department of Radiobiology/Molecular Epidemiology, RERF

*This article is based on the following publication:

Kengo Yoshida, Eiji Nakashima, Yoshiko Kubo, Mika Yamaoka, Junko Kajimura, Seishi Kyoizumi, Tomonori Hayashi, Waka Ohishi, Yoichiro Kusunoki: Inverse Associations between Obesity Indicators and Thymic T-cell Production Levels in Aging Atomic-bomb Survivors, *PLoS ONE* 2014 (March); 9(3):e91985 (doi: 10.1371/journal.pone.0091985)

Study Findings

T-cell receptor excision circles, or TRECs, are circular molecules of DNA excised from chromosomes when T cells are produced in the thymus. They indicate new production of T cells, and their numbers, which decrease with aging, represent an immunological marker of thymic capacity to produce naïve T cells. In this study, low TREC numbers were found to be associated with diseases related to high body mass index (BMI) and obesity, such as diabetes and fatty liver. These results suggest the possibility that reduction of immunological competence associated with aging may be further accelerated by obesity.

Explanation

The production of T cells, which are blood cells with immunological functions, starts in the bone

marrow and then continues in the thymus. In previous immunological studies at the Radiation Effects Research Foundation (RERF), the number of naïve T cells in peripheral blood was found to decrease after radiation exposure, leading to a hypothesis describing the mechanism behind this decline as the effect of radiation exposure on the ability of the thymus to produce naïve T cells.

Based on animal model studies conducted in recent years, obesity has been linked to the functional decline of the T-cell immune system associated with aging. However, findings based on studies of human populations were extremely limited.

We therefore conducted a study of RERF's Adult Health Study (AHS) participants, whose health has been followed for many years, in order to determine the effects of age, radiation dose, and obesity on indicators of thymic capacity to produce

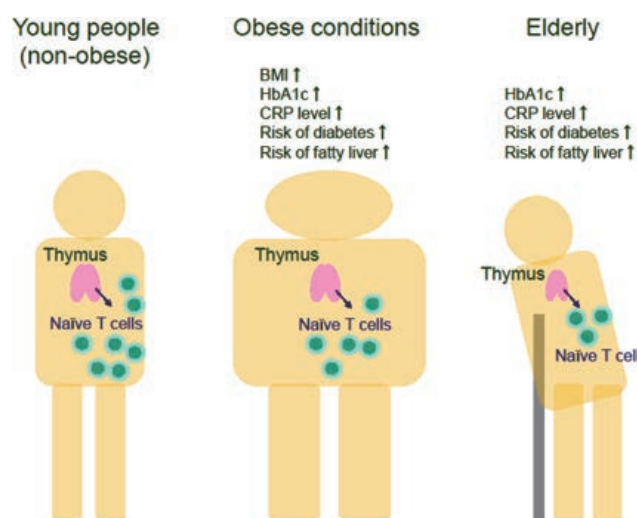


Figure. Relationship of naïve T-cell production levels to aging and obesity

naïve T cells (TREC number).^{Note}

Note) TRECs, excised from chromosomes when T cells are produced in the thymus, are by-products of this process and characteristic of newly produced naïve T cells. Because they are not replicated by subsequent cell divisions in blood, TREC number can be used as an indicator of thymic capacity to produce naïve T cells.

1. Objectives

The objectives of the study were to examine the relationship between radiation exposure and TREC number, an indicator of thymus capacity to produce naïve T cells, and to determine the association of TREC number to obesity indicators and diseases associated with obesity, after adjusting for the effects of age, sex, radiation exposure, alcohol consumption, and smoking.

2. Methods

Among 1,073 A-bomb survivors who participated in the AHS from 2003 to 2009, we measured TREC number per 10,000 CD4 T cells (helper T cells, which control immune response) and per 10,000 CD8 T cells (killer T cells, which detect and destroy infected or transformed cells) in peripheral blood, utilizing polymerase chain reaction. We used information obtained from the AHS on BMI as an indicator of obesity, total cholesterol level, HbA1c level (which represents blood glucose levels over the previous 2–3 months), and CRP level (an indicator of inflammation), as well as diseases related to obesity (type 2 diabetes, fatty liver, and hypertension), alcohol consumption, and smoking. We conducted linear regression statistical analysis, with adjustment made for age, sex, radiation dose, amount of alcohol consumed, and number of cigarettes smoked.

3. Results

(1) Relationship between TREC number and age

Subject ages ranged from 58 to 109 years. Even in this elderly population, TREC number in CD4 and CD8 T cells decreased with age ($p < 0.001$ in terms of significance).

(2) Relationship between TREC number and radiation dose

Radiation exposure had no effect on TREC number in either CD4 or CD8 T cells. We also conducted a preliminary analysis by selecting, from among the 1,073 subjects, a high-dose group (radiation dose of at least 1 Gy) and a control group (radiation dose of less than 5 mGy), matched by such factors as age and sex, and then comparing the two groups. No difference in TREC number was observed in relation to radiation dose.

(3) Association between TREC number and obesity indicators

TREC number in CD4 and CD8 T cells significantly decreased with an increase of HbA1c and CRP levels ($p < 0.05$). TREC number also tended to be inversely associated with BMI. Further, TREC number was small in cases of diabetes and fatty liver ($p < 0.05$).

In this study, no association between TREC number and radiation exposure was observed, but TREC number was found to decrease with an increase in the levels of obesity indicators in a human population. This result provides evidence to suggest that obesity may accelerate immunological aging in humans. Because obesity is known to increase the risk of several age-related diseases, attenuated immune competence due to the reduction in naïve T-cell production may be one of the developmental mechanisms of diseases associated with obesity.

A Novel *RET* Rearrangement (*ACBD5/RET*) by Pericentric Inversion, *inv(10)* (p12.1;q11.2), in Papillary Thyroid Cancer from an Atomic-bomb Survivor Exposed to High-dose Radiation*

Kiyohiro Hamatani

Department of Radiobiology/Molecular Epidemiology, RERF

*This article is based on the following publication:

Kiyohiro Hamatani, Hidetaka Eguchi, Kazuaki Koyama, Mayumi Mukai, Kei Nakachi, and Yoichiro Kusunoki: A Novel *RET* Rearrangement (*ACBD5/RET*) by Pericentric Inversion, *inv(10)* (p12.1;q11.2), in Papillary Thyroid Cancer from an Atomic-bomb Survivor Exposed to High-dose Radiation. *Oncol Rep* 2014 (August); 32:1809–14 (doi: 10.3892/or.2014.3449)

Study Findings

Our analysis has shown that a novel type of *RET* rearrangement (*ACBD5-RET* fusion gene) that was identified in papillary thyroid cancer (PTC) cells of an atomic bomb survivor constitutively activates the MAPK-signaling pathway* and can lead to the development of tumors, as is the case with other types of *RET* fusion genes.

*The term “signaling pathways” denotes the mechanism by which protein kinases phosphorylate (in other words, activate) other protein kinases and cascade signals downstream. The MAPK-signaling pathway is one such pathway.

Explanation

Through chromosomal inversion or translocation, radiation-related PTC cases such as adult PTC among A-bomb survivors and childhood PTC that developed after the Chernobyl nuclear accident often exhibit rearranged *RET* genes, that is fusion genes such as *CCDC6-RET* and *NCOA4-RET*, between the *tyrosine kinase domain* of the *RET* gene and other gene sites. These fusion genes are believed to be significantly involved in papillary thyroid carcinogenesis.

We analyzed the structure and function of a novel *RET* rearrangement (*ACBD5-RET* fusion gene) found in the PTC of an A-bomb survivor exposed to high-dose radiation.

1. Objectives

To elucidate, through *in vitro* and *in vivo* experiments, whether the *ACBD5-RET* fusion gene found in the PTC of the A-bomb survivor activates the MAPK-signaling pathway and induces tumor for-

mation.

2. Methods

(1) Expression vectors, i.e., plasmid DNA with a promoter sequence needed for gene expression, containing cDNA (DNA synthesized from an RNA template by reverse transcriptase and complementary to mRNA) of the *ACBD5-RET* fusion gene were introduced into mouse *NIH3T3* cells (immortalized fibroblasts established from mouse skin cells). This process was undertaken to determine, using Western-blotting*, whether phosphorylation (or, activation) of protein kinase in the MAPK-signaling pathway is enhanced.

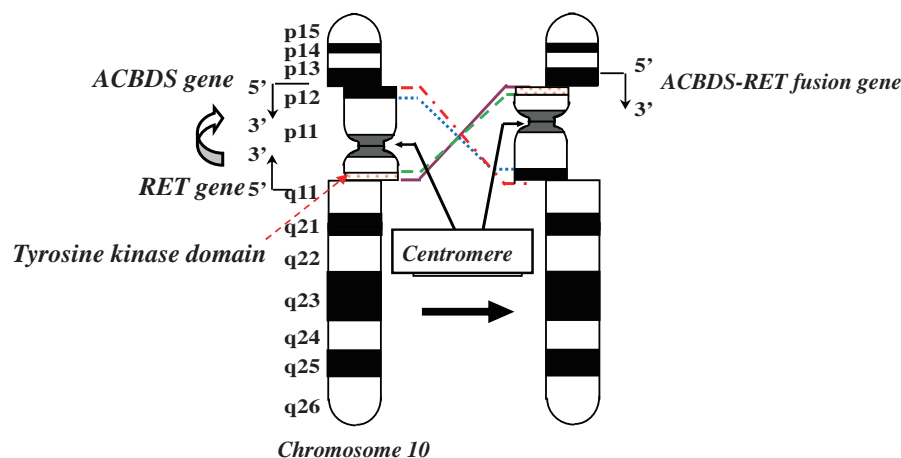
*Western-blotting is an analytical technique for detecting specific proteins. It uses gel electrophoresis to separate protein samples, transfers and fixes them to a membrane (filter paper for blotting), and identifies specific proteins based on antigen-antibody reactions.

(2) We introduced the cDNA of the *ACBD5-RET* fusion gene into *NIH3T3* cells, injected the resultant *NIH3T3* cells subcutaneously into nude mice, and examined tumor formation to evaluate the tumorigenicity of the *ACBD5-RET* fusion gene.

3. Results

(1) We determined that the *ACBD5-RET* fusion gene is formed via inverse binding between a break point in the *tyrosine kinase domain* of the *RET* gene located in the long arm of chromosome 10 and the 5' end of the *ACBD5* gene located in the short arm of the same chromosome (pericentric inversion) (see Figure).

Figure (Inversion)



This figure shows the *ACBDS-RET* fusion gene formed by a pericentric inversion. Inversions occur when a chromosome breaks in two places and the resulting fragment of DNA is inverted and re-inserted into the chromosome. Inversions that involve the centromere (the constricted region of the chromosome) are called pericentric inversions.

- (2) Accelerated phosphorylation of protein kinase was observed in the *NIH3T3* cells with an *ACBDS-RET* fusion gene.
- (3) After injection into the nude mice, the *NIH3T3* cells with an *ACBDS-RET* fusion gene continued proliferating and formed tumors.

This study showed that the *ACBDS-RET* fusion gene found in the PTC of an A-bomb survivor is

significantly involved in papillary thyroid carcinogenesis, as is the case with other *RET* fusion genes such as *CCDC6-RET* and *NCOA4-RET*. *RET* gene rearrangement induced either directly or indirectly by radiation is therefore suggested to be closely involved in papillary thyroid carcinogenesis among PTC patients exposed to relatively high doses of radiation.

Linkage between Dendritic and T-cell Commitments in Human Circulating Hematopoietic Progenitors*

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*This article is based on the following publication:

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Study Findings

Dendritic cells (DCs) play an indispensable role in the differentiation and functional expression of T cells. These two types of cells differentiate from hematopoietic stem cells (HSCs), and the current study finds that the frequencies of T-cell and DC precursors are significantly linked with each other in stem cells existing in blood, whereas they are not linked to the precursor frequency (PF) of natural killer (NK) cells.

Explanation

1. Objectives

DCs are a type of leukocyte with dendrites. They initiate an adaptive immune response by conveying antigen information about viruses and bacteria that have invaded the body to T cells, which serve as a 'control tower' for the adaptive immune response. DCs also prevent the generation of self-antigen-responsive T cells in the thymus as a negative selection. Because self-antigen-responsive T cells recognize substances that make up their host body as antigens, these cells are detrimental. DCs are thus essential for the differentiation and functional expression of T cells. Based on this understanding, we hypothesized that there may be a correlation between the potency of HSCs to differentiate into DCs and their potency to differentiate into T cells, suggesting a linkage between DC and T-cell commitments. (HSCs are the least differentiated cells that can give rise to all blood cell types, are long lived, and have the ability to self-replicate.) Verifying this hypothesis was considered to provide important findings for ongoing studies of A-bomb survivors involving T-cell progenitors and DCs. DCs can be classified as conventional DCs (cDCs, which inform T cells of antigens to initiate direct attack) or plasmacytoid DCs (pDCs, which pro-

duce type-I interferon and induce anti-viral infection immunity). In the present study, we analyzed DC progenitors of both types.

2. Methods

It is possible to separate hematopoietic progenitor cells (HPCs, cells with the potency to differentiate into T cells and DCs) in human peripheral blood using a cell sorter, and then to differentiate HPCs into T cells and NK cells using the culture method reported in Kyoizumi *et al.*: *J Immunol* 2013; 190:6164–72. NK cells are a type of cytotoxic lymphocyte that is important for the innate immune system. Since the present study confirmed that this culture method could induce differentiation of HPCs into DCs, we used it as an experimental system to simultaneously assay T cells, NK cells, and DC progenitors. Blood samples were collected, based on informed consent, from 20 RERF in-house volunteer donors aged 26–65 years, and we measured the PFs of T cells and NK cells, as well as cDCs and pDCs, based on the culture method, to examine correlations among the PFs of these cells. Furthermore, we examined the potencies of single precursor cells to differentiate into T cells and NK cells, as well as cDCs and pDCs, based on precursor cell clonal culture.

3. Results

- (1) The PFs of cDCs and pDCs in HPCs were found to correlate significantly with T-cell PFs, but not with NK-cell PFs.
- (2) The precursors producing T cells and NK cells were classified into clones producing T/NK dual-, T single-, and NK single-lineage precursors. The clones of T/NK dual- and T single-lineage precursors produced cDCs or pDCs at high frequencies. The clones of NK single-lin-

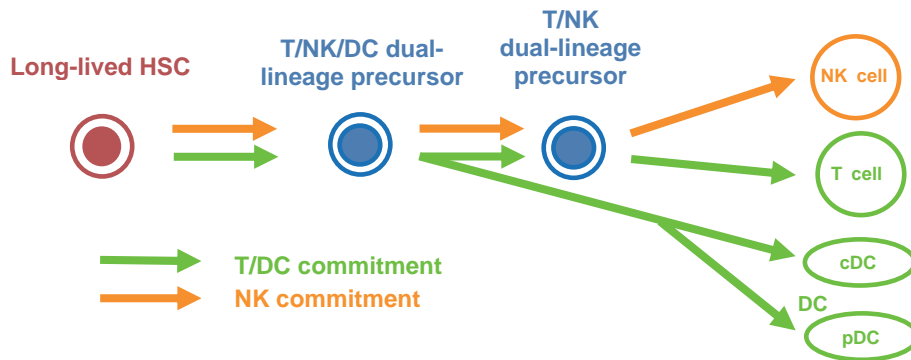
age precursors, however, produced very few cDCs or pDCs.

4. Consideration and Conclusion

These findings show that T-cell and DC commitments are linked with each other, as indicated with the green lines below. On the other hand, this research suggests that NK-cell commitment is induced independently from DC commitment.

In addition, the linkage between T-cell and DC precursors might be intrinsically imprinted in long-lived HSCs existing in bone marrow that are self-replicating, since the T-cell and DC progenitors in the human body have short life spans.

Note: Progenitors are specific cells, generated from stem cells, that are able to differentiate into more specific types of cells.



George Takei Visits Hiroshima RERF for Filming of *Takei's Take* Involving Technology in Japan

On June 10, 2014, the Radiation Effects Research Foundation (RERF) in Hiroshima was very fortunate to host George Takei and his film and support crew while they filmed a segment for his series of AARP-sponsored YouTube videos, *Takei's Take*.

Mr. Takei is a director, author, and actor, originally known for his role as Lt. Sulu in the American television series *Star Trek*, which first aired in the late 1960s. More recently, Mr. Takei's involvement in social media has brought him huge numbers of followers, due to frequent postings of social commentary and humor on his Facebook and Twitter accounts. He has been involved in politics, championed gay rights and other issues, and won several awards for his work on human rights and Japanese-American relations, including his work with the Japanese American National Museum, located near the downtown area of Los Angeles.

In this season of the series, Mr. Takei traveled around the globe to explore and experience technology that is changing the world. We were thankful that he chose to stop by RERF for a feature series on Japan, which included an interview with Dr. Harry M. Cullings, Chief, Department of Statistics, related to a revised mapping system for more accurately identifying survivor locations at the time of the atomic bombings.

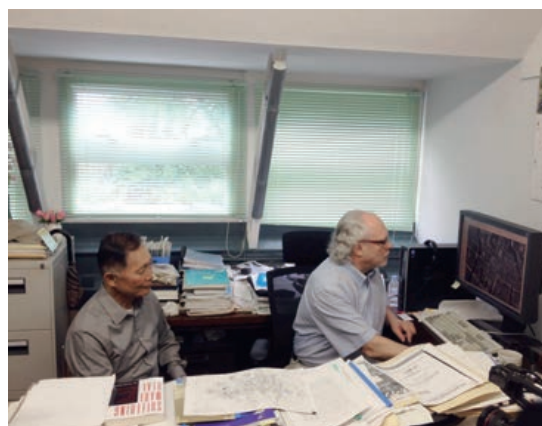
Dr. Cullings explained to Mr. Takei and his crew the key advantages of Geographical Information System (GIS) technology, which is used at RERF to obtain more precise locations of survivors at the time of the bombings and thus enable more accurate assessment of the radiation doses that the survivors received.

For Mr. Takei, though, the visit to RERF was also personal: some of his relatives survived the atomic bombing of Hiroshima. In the second in this series of videos, Dr. Cullings shows by GIS image the estimated locations of Mr. Takei grandparents' and aunt's homes in Hiroshima at the time of the A-bombing of that city (see photo at right). Mr. Takei goes on to describe the destructive power of the atomic bombs and their impact on the lives of his own relatives. In the third episode, Mr. Takei, together with his cousin, try to locate their grandparents' home, only to fall short of identifying the

exact location due to development of the city that has taken place since the A-bombing of Hiroshima on August 6, 1945.

To view all four of Mr. Takei videos about Japanese technology and his thoughts about both historical and modern-day Japan, please access them through Facebook at "Radiation Effects Research Foundation" or by clicking the Facebook page link on the front page of our website.

RERF studies the effects of radiation on health in the hope that, in the future, radiation technology will only be used for peaceful purposes. We are profoundly grateful to Mr. Takei for his efforts to help us more broadly convey information about the work taking place at RERF.



Dr. Harry Cullings, Chief, Statistics Dept., explaining GIS technology to George Takei (left) during interview



GIS image showing locations of the homes (represented by red circles) of George Takei's relatives

Neutrons from the Atomic Bombs in Hiroshima and Nagasaki

Harry M. Cullings, Chief
Department of Statistics

The direct radiations from the atomic bombs in Hiroshima and Nagasaki, which are the basis of the dose estimates for individual survivors that are used in all RERF studies, consisted of neutrons and gamma rays. Although for each survivor the amount of energy deposited in the body (absorbed dose) from neutrons was much less than that from gamma rays, there has been enduring concern about neutrons, because it is well known that neutrons create more biological effect per unit of absorbed dose than do gamma rays (greater radiobiological effectiveness, or “RBE”). Here we give some key numbers related to neutrons, particularly relative to gamma rays, which may be helpful in forming a numerical perspective on the importance of neutron vs. gamma-ray dose for the atomic bomb survivors.

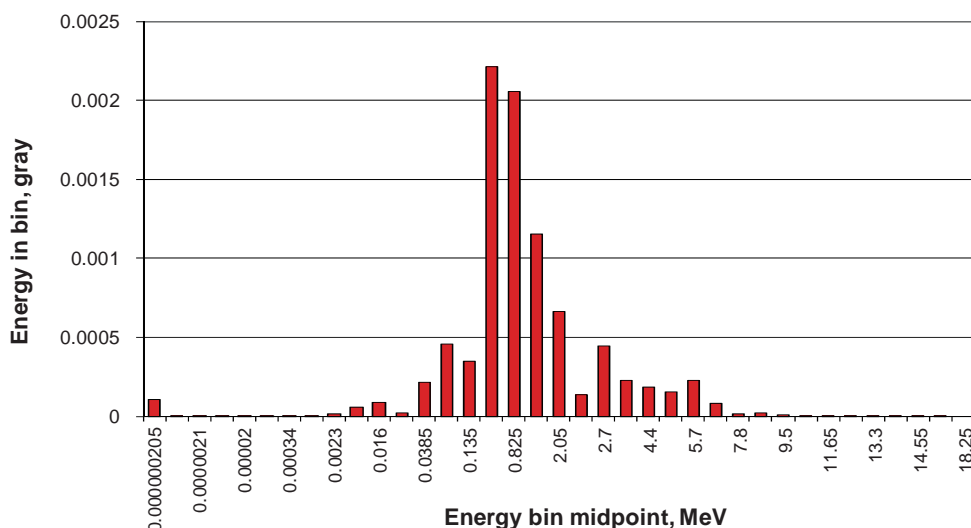
The number of neutrons and gamma rays passing through a given cross-sectional area was very large: for example, at 1.5 km from the hypocenter in Hiroshima there were about 2.2 billion neutrons and 155 billion gamma rays per square centimeter of cross-sectional area, or about 70 times as many gamma rays as neutrons.¹ However, as large as these numbers may sound, absorbed dose to a small

mass of tissue suspended in air represented only about 9 mGy from neutrons and 530 mGy from gamma rays.² The energy distribution of neutrons in Hiroshima is shown in the figure, for intervals of energy into which neutrons are grouped for computational purposes in DS02 (“energy bins”). It can be seen that most of the dose is associated with neutrons in the energy range of about 0.5 to 2 MeV.

Because neutrons are more rapidly attenuated by passage through air than are gamma rays, the neutron absorbed dose to a small mass of tissue suspended in air, as a % of the gamma-ray dose, decreases with distance. It ranges from about 5% at 1 km in Hiroshima to about 0.2% at 2.5 km.³ In addition, although gamma rays are not attenuated much by the human body, neutrons are strongly attenuated by the body because of mechanical collisions between neutrons and the protons that constitute nuclei of the hydrogen atoms in tissue. Thus, the neutron dose as a fraction of gamma-ray dose for a deep organ such as the colon is much smaller than for a superficial organ such as the skin or the lens of the eye, ranging from < 1% at 1 km to about 0.03% at 2.5 km.³

In Nagasaki, neutron doses as a fraction of

Energy Distribution of Hiroshima Neutron Free-In-Air Kerma at 1500 m



gamma-ray doses tend to be several times smaller than in Hiroshima. Thus, it is really only the most proximal survivors (those nearest the hypocenter) in Hiroshima who had neutron doses that equaled a substantial fraction of their gamma-ray doses.

All of these considerations about the small size of neutron doses relative to gamma-ray doses are offset to some extent by the RBE that is typically used for neutrons. RERF has tended to use a constant RBE of ten (10) in most of its major publications, but constant values as high as twenty (20) have been advocated by some investigators. Furthermore, dose-dependent RBEs that take on values approaching 100 at very low doses and decrease with increasing dose have been advocated, based on the curvature in the gamma-ray dose response for many biological endpoints in experimental radiation biology. However, at the low doses where such large values of the variable RBEs would apply, the neutron doses received by survivors were extremely small relative to the gamma-ray doses, as indicated above. Therefore, the choice of RBE among the alternatives just described does not have a major effect on risk estimates, as explained in

detail in a new paper recently published in *Radiation Research*.⁴

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